Donor Characteristics Affecting Graft Failure, Graft-versus-Host Disease, and Survival after Unrelated Donor Transplantation with Reduced-Intensity Conditioning for Hematologic Malignancies

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We examined the effect of donor characteristics on graft failure (<5% donor chimerism within 3 months after transplantation), acute and chronic graft-versus-host disease (aGVHD, cGVHD), and survival after unrelated donor reduced-intensity conditioning (RIC) transplantation in 709 patients with hematologic malignancies. Donor–recipient pairs were HLA typed at HLA-A, -B, -C, and -DRB1 (allele-level). A total of 501 patients were >95% donor chimerism, 145 patients were 5% to 95%, and 63 patients were <5%. The only donor characteristic associated with transplantation outcome was donor–recipient HLA matching. One- or 2-loci mismatched transplants led to higher grade 2-4 (relative risk [RR] = 1.27, $P = .035$) and grade 3-4 (RR = 1.85, $P < .001$) aGVHD and 2-loci mismatched transplants higher mortality (RR = 2.22, $P < .001$). Graft failure was higher after transplantation of bone marrow (RR = 2.33, $P = .002$). Donor age, parity, and donor sex match were not associated with transplantation outcome. Donor–recipient HLA matching is the only donor characteristic predictive for survival after RIC regimens for hematologic malignancies.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a curative option for malignant and nonmalignant diseases [1]. The last decade has seen an expansion of HSCT, in part because of use of reduced-intensity conditioning (RIC) regimens making that have made this treatment option available to the elderly and patients with comorbidities who are unlikely to tolerate myeloablative conditioning regimens [2-4]. RIC regimens now account for approximately 40% of allogeneic transplantations in adults with hematologic malignancies. The characteristics of donors that influence HSCT outcomes after myeloablative conditioning regimens are described [5,6]. However, little is known about the effect of unrelated adult donor (URD) characteristics on the outcomes of RIC HSCT. Therefore, using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), we examined the association between donor characteristics and outcomes after URD HSCT with RIC regimens for hematologic malignancies.

MATERIALS AND METHODS

Patients

Included are 709 patients with hematologic malignancies (Table 1) who received an RIC regimen for their first URD transplantation from 1999 to 2006 in the United States, and facilitated by the National Marrow Donor Program. The preparative regimen was considered RIC when patients received busulfan <9 mg/kg, melphalan <150 mg/m^2, and total body

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Table 1. Patient, Disease, and Transplant Characteristics

Variables	Number (%)
Total	709
Patient age (years)	
18-30	37 (5)
31-40	63 (9)
41-50	113 (16)
51-60	302 (43)
>60	194 (27)
Performance score	
90-100	417 (59)
<90	223 (31)
Not reported	69 (10)
Disease	
Acute myeloid leukemia	353 (50)
Acute lymphoid leukemia	37 (5)
Myelodysplastic syndrome	74 (10)
Chronic myeloid leukemia	70 (10)
Non-Hodgkin lymphoma	175 (25)
Disease status at transplantation	
First complete remission, chronic phase, refractory anemia	253 (36)
Second complete remission, chronic phase, accelerated phase	222 (31)
Not in remission, refractory anemia with excess blasts or in transformation	234 (33)
Graft source	
Peripheral blood progenitor cells	550 (78)
Bone marrow	159 (22)
Conditioning regimen	
Irradiation-containing*	209 (29)
Busulfan-containing†	188 (27)
Melphalan-containing‡	217 (31)
Cyclophosphamide-containing§	95 (13)
Graft-versus-host disease prophylaxis	
Tacrolimuscontaining regimens¶	419 (59)
Cyclosproinecontaining regimens‖	290 (41)
Donor age (years)	
18-30	233 (33)
31-40	277 (39)
41-50	165 (23)
51-60	34 (5)
Donor-recipient HLA match**	
Matched at HLA-A, -B, -C, -DRB1	498 (70)
1-locus mismatch	170 (24)
2-loci mismatch	41 (6)
Donor-recipient sex match††	
Male donor to male recipient	282 (40)
Male donor to female recipient	189 (27)
Female donor to male recipient	127 (18)
Female donor to female recipient	111 (16)
Donor-recipient cytomegalovirus serostatus	
Negative donor to negative recipient	198 (28)
Negative donor to positive recipient	270 (38)
Positive donor to negative recipient	70 (10)
Positive donor to positive recipient	161 (23)
Unknown	10 (1)
Donor-recipient ABO match	
Matched	286 (40)
Minor ABO incompatibility	182 (26)
Major ABO incompatibility	241 (34)

*Irradiation-containing.
Total body irradiation (TBI) (200 cGy, single fraction) + fludarabine ± antithymocyte globulin (ATG)/monoclonocal antibody (n = 166).
TBI (200 cGy, single fraction) + ATG (n = 8).
TBI (200 cGy, single fraction) + busulfan (n = 2).
TBI (300 cGy, 400 cGy or irradiation 450 cGy, single fraction) + fludarabine ± busulfan (n = 18).
TBI (400 cGy, fractionated) + fludarabine + busulfan (n = 13).
TBI (400 cGy, fractionated) + fludarabine (n = 2).
†Busulfan-containing.
Busulfan + fludarabine + ATG/monoclonal antibody (n = 93).
Busulfan + fludarabine (n = 24).
Busulfan + cylcophosphamide + ATG (n = 4).
Busulfan + cylcophosphamide (n = 42).
Busulfan + fludarabine + total lymphoid irradiation (n = 25).
‡Melphalan-containing
Melphalan + fludarabine (n = 108).
Melphalan + fludarabine + ATG/monoclonal antibody (n = 98).
Melphalan + other agents (n = 11).
§Cyclophosphamide-containing
Cyclophosphamide + fludarabine (n = 39).
Cyclophosphamide + fludarabine + ATG/monoclonal antibody (n = 44).
Cyclophosphamide + other agents (n = 12).
¶Tacrolimus-containing regimens
Tacrolimus alone (n = 47).
Tacrolimus + mycophenolate mofetil (n = 127).
Tacrolimus + methotrexate (n = 245).
‖Cyclosporin-containing regimens
Cyclosporin alone (n = 37).
Cyclosporin + mycophenolate mofetil (n = 178).
Cyclosporin + methotrexate (n = 75).
**Matching at DQ was not considered as a single mismatch at this locus and is not associated with adverse outcome [5].
††Among female donors, n = 97 are nulliparous, n = 132 have had 1 or more pregnancies, and parity was not reported for 9 patients.

irradiation (TBI) 200 cGy single dose or >200 to 450 cGy (single or fractionated dose) [7]. Patients received either bone marrow (BM) or peripheral blood progenitor cells (PBPC). The decision to offer the RIC regimen and the choice of graft type was at the discretion of the transplant center. Allele-level HLA typing at -A, -B, -C, and -DRB1 were available for all donor–recipient pairs; donor–recipient HLA typing was performed at a central laboratory. Mismatches at intermediate (antigen) or high (allele) resolution were considered equivalent and were described as allele-mismatches [5]. Excluded were patients aged <18 years, those who had received a prior autologous or allogeneic transplantation, T cell-depleted BM and CD34 selected PBPC and recipients of cord blood grafts. The study was approved by the institutional review boards of the Medical College of Wisconsin and the National Marrow Donor Program.

Endpoints

Primary endpoints were graft failure defined as the absence of absolute neutrophil count $\geq 0.5 \times 10^9$/L or donor chimerism <5% within 3 months posttransplantation without clinical relapse for patients with absolute neutrophil count $\geq 0.5 \times 10^9$/L and overall survival. For patients with chimersim assay <95% and >5% (mixed donor chimerism), subsequent assay confirmed <5% (graft failure) or >95% (full donor chimerism). Chimerism assays were performed on BM or whole blood without taking cellular subsets into account; the timing and method of assay was at the discretion of the transplant center. The median time to chimerism assay was 1.5 months (range: 0.9-3.0). In 79 patients (11%), the method employed

was fluorescent in situ hybridization, and for the remaining patients, molecular methods. Secondary endpoints were acute grade 2-4, grade 3-4 graft-versus-host disease (GVHD), and chronic GVHD (cGVHD) [8,9].

Statistical Methods

Patient, disease, donor, and transplant characteristics are shown in Table 1. The probability of overall survival (OS) was calculated using the Kaplan-Meier estimator [10]. Death from any cause was an event, and surviving patients were censored at last follow-up. A logistic regression model was constructed to identify risk factors for graft failure at 3 months, and the Cox model, for acute GVHD (aGVHD), cGVHD, and overall mortality [11]. Models were built using forward step-wise selection and variables shown in Table 1, which attained a significance level of ≤ 0.05 retained in the final model. All P values are 2 sided. The effect of transplant center on OS was tested using the frailty method [12]. All analyses were done using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS AND DISCUSSION

Our primary objective was to identify the effect of donor characteristics on graft failure, aGVHD and cGVHD, and survival to allow selection of the optimal URD for RIC-HSCT in patients with hematologic malignancies. The median follow-up of surviving patients is 2.5 years. Donor-recipient matching considered matching at HLA-A, -B, -C, and -DRB1 (allele-level typing). A total of 501 patients were >95% donor chimerism, 145 patients 5%-95% (mixed chimerism), and 63 patients <5% (graft failure). Graft failure rates were higher after transplantation of BM compared with PBPC (odds ratio [OR]: 2.33, 95% confidence interval [CI]: 1.35-4.01, P = .002). No other characteristic was associated with graft failure. Transplantation of BM was not associated with higher mortality risks despite the higher risk of graft failure. In the 145 patients with mixed donor chimerism, 101 had recurrent disease, which ultimately resulted in graft failure; the median time to recurrent disease was 57 days from transplantation. Eighteen patients with mixed donor chimerism died from transplant-related complications. Only 26 patients are alive and disease-free at last follow-up. Forty-five of 63 patients with graft failure (<5% donor chimerism) are dead (recurrent disease or organ failure) and 18 are alive; 10 of these patients are in remission. Despite higher graft failure rates associated with transplantation of BM, graft type was not associated with OS; 28 of 39 (72%) PBPC recipients and 17 of 24 (71%) are dead. Patients with graft failures received alternative therapies and our data suggest salvage rates do not differ by graft type for first transplantation. Consequently, in the current analysis, graft type was not associated with OS.

Consistent with reports after myeloablative conditioning regimens for hematologic malignancies [5], risks of acute grade 2-4 and grade 3-4 aGVHD were higher after transplantations mismatched at 1- or 2-loci (Table 2). Risks of acute 2-4 and grade 3-4 GVHD were lower with in vivo T cell depletion. Grade 3-4 aGVHD was lower with tacrolimus-containing GVHD prophylaxis regimens. Chronic GVHD was not associated with HLA mismatch, and this was consistent with reports after myeloablative transplant conditioning [5]. Chronic GVHD was lower with in vivo T cell depletion regimens (Table 2). We examined for an effect of in vivo T cell depletion on survival and found none. Our findings differ from a recent CIBMTR report [13]; use of antithymocyte globulin (ATG) was associated with significantly lower survival in recipients of non-TBI conditioning regimens. That report had almost 800 patients who received in vivo T cell depletion compared with the 419 patients in the current analysis, and differences in sample size likely account for the observed difference between the 2 reports.

The only donor characteristic affecting OS was donor–recipient HLA mismatch (Table 2 and Figure 1). Compared with matched transplants, mortality risks were higher after transplantations mismatched at 2-loci but not for transplantations mismatched at 1-locus. Only 170 donor–recipient pairs were mismatched at 1-locus, and the relatively small sample size may explain our inability to detect a significant difference. Mortality risks were also higher after 2-loci mismatched transplantations compared to 1-locus mismatched transplantations (relative risk [RR] = 1.88, 95% CI: 1.27-2.78, P = .002). We considered donor–recipient matching at HLA-A, -B, -C, and -DRB1. Although we did not consider matching at HLA-DQ, typing was available for 90% of donor–recipient pairs (N = 641), and most pairs (N = 577; 90%) were matched at this locus. Death from infection, interstitial pneumonitis, and organ failure were more likely after 1- and 2-loci mismatched transplantations compared with matched transplantations. Disease status at transplantation is a predictor of mortality and a modifiable factor for many patients through early referral for HSCT. Mortality rates were higher when patients were not in remission at transplantation (RR = 1.42, 95% CI: 1.16-1.74, P < .001). This effect is independent of donor–recipient HLA mismatch. Patients >60 years old (RR = 1.41, 95% CI: 1.13-1.76, P = .002) and those with a performance score <90 at transplantation (RR = 1.39, 95% CI: 1.12-1.71, P = .003) experienced higher mortality.

We specifically explored for an effect of donor age, donor–recipient sex match, cytomegalovirus (CMV)

Table 2. Results of Multivariate Analysis

Outcome	Hazard Ratio (95% Confidence Interval)	*P* Value
Grade 2-4 acute GVHD		
Donor-recipient HLA match		
Matched at HLA-A, -B, -C, -DRB1	1.00	
Mismatched at 1 or 2 HLA-loci	1.32 (1.05-1.65)	.015
In vivo T cell depletion		
Non-TBI regimens with in vivo T cell depletion	1.00	
TBI regimens without in vivo T cell depletion	1.64 (1.23-2.18)	.0007
Non-TBI regimens without in vivo T cell depletion	1.73 (1.34-2.24)	<.0001
TBI regimens with in vivo T cell depletion	1.03 (0.59-1.80)	.92
Grade 3-4 acute GVHD		
Donor-recipient HLA match		
Matched at HLA-A, -B, -C, -DRB1	1.00	
Mismatched at 1 or 2 HLA-loci	1.87 (1.34-2.60)	.0002
In vivo T cell depletion		
Non-TBI regimens with in vivo T cell depletion	1.00	
TBI regimens without in vivo T cell depletion	1.23 (0.76-2.00)	.39
Non-TBI regimens without in vivo T cell depletion	1.75 (1.17-2.61)	.006
TBI regimens with in vivo T cell depletion	1.01 (0.42-2.39)	.99
GVHD prophylaxis		
Cyclosporine-containing regimens	1.00	
Tacrolimus-containing regimens	0.65 (0.46-0.92)	.014
Chronic GVHD		
In vivo T cell depletion		
Non-TBI regimens with in vivo T cell depletion	1.00	
TBI regimens without in vivo T cell depletion	2.35 (1.76-3.14)	<.0001
Non-TBI regimens without in vivo T cell depletion	2.18 (1.67-2.84)	<.0001
TBI regimens with in vivo T cell depletion	1.48 (0.81-2.70)	.20
Overall mortality		
Donor-recipient HLA match		
Matched at HLA-A, -B, -C, -DRB1	1.00	
Mismatched at 1 HLA-locus	1.18 (0.94-1.48)	.15
Mismatched at 2 HLA-loci	2.34 (1.62-3.37)	<.0001
Recipient age		
18-50 years	1.00	
>50 years	1.31 (0.105-1.65)	.018
Recipient performance score		
90-100	1.00	
≤80	1.39 (1.12-1.72)	.003
Disease status at transplantation		
Remission	1.00	
Relapse or primary induction failure	1.51 (1.23-1.85)	<.0001

TBI indicates total body irradiation; GVHD, graft-versus-host disease.

serostatus, and ABO compatibility and did not find an association among these characteristics and graft failure, GVHD, or survival. Our findings are consistent with a recent report that considered donor–recipient matching at the allele-level for HLA-A, -B, -C, and -DRB1 after URD HSCT with myeloablative conditioning for hematologic malignancies [5]. A likely explanation for our inability to detect differences in HSCT outcomes by donor age could be because of the fact that only 5% of donors were older than 50. Although the National Donor Marrow Program guideline limit for donor age is 18 to 60 years, the current study population suggests that approximately 70% of adult donors called to donate are 18 to 40 years old. The selection of younger donors by transplant physicians effectively prevents us from further exploring the effect of donor age on transplantation outcomes. Others have shown that GVHD and mortality risks are higher in male recipients of female donors when the donor is a matched sibling [14], and, more recently, these findings were confirmed in another report [15]. In that report [15], 75% of transplantations used were matched sibling donors, most received myeloablative conditioning regimens, and the observed effect

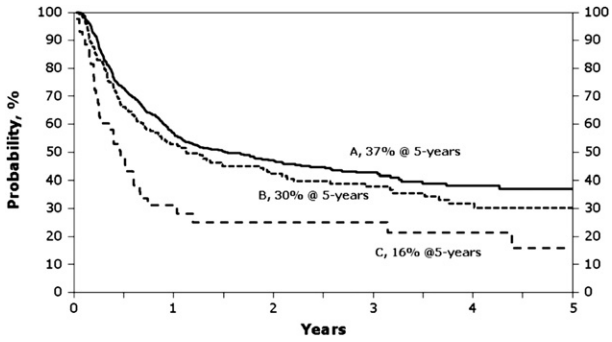

Figure 1. Probabilities of OS after HLA-matched (A), 1-locus mismatched (B), and 2-loci mismatched (C) unrelated donor transplantation adjusted for patient age, performance score, and disease status at transplantation. The 5-year probabilities are 37% (95% CI: 32-42), 30% (95% CI: 22-38), and 16% (95% CI: 6-31) after HLA-matched, 1-locus mismatched, and 2-loci mismatched unrelated donor transplants, respectively.

of donor–recipient sex match was most pronounced for chronic myeloid leukemia (CML) and myeloma. Our inability to observe an effect of donor–recipient sex match on HSCT outcomes may be explained by differences in the study population. Our report is limited to recipients of URD HSCT with RIC regimens, donor–recipient matching considered allele-level HLA typing at HLA-A, -B, -C, and -DRB1, only 10% of patients in the current analysis had CML and there were no patients with myeloma. Patients with myeloma were excluded, because URD HSCT is not considered first-line treatment. Importantly, our observations are consistent with a large series on URD HSCT with myeloablative conditioning regimens [5].

Our findings have important implications for selecting adult unrelated donors when considering RIC regimens for patients with hematologic malignancies. Survival rates are highest with donor–recipient pairs matched at HLA-A, -B, -C, and -DRB1. Avoiding transplantation of bone marrow grafts and transplantation of PBPCs will lower graft failure rates.

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AUTHORSHIP STATEMENT

J.R.P., M.J.Z., V.R., and M.E. designed the study. J.R.P. and M.E. interpreted results and wrote the manuscript. M.J.Z. and F.K. performed the statistical analysis and interpreted results. V.R., R.E.C., L.M.I., A.P.G., J.G., M.J.L., H.M.L., A.L., D.I.M., and A.G. interpreted results and critically revised the manuscript. The authors have no conflicts of interest to declare.

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